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Review

Tumor Cell Secretomes in Response to Anti- and Pro-Tumorigenic Agents

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Abstract: Tumor cells regulate their progression not only by the factors within their cell bodies but also by the secretome they produce and secrete. While their secretome significantly alters the fate of tumor cells themselves, they also regulate the growth of surrounding cells including both companion cancer and non-cancer cells. Tumor cell secretome consists of varying molecules that have been reported mostly tumor-promotive. Furthermore, their pro-tumor capability is enhanced by the application of chemotherapeutic agents. However, multiple lines of emerging evidence suggest that the tumor cell secretome can be tumor-suppressive in response to paracrine and endocrine signaling. This review introduces both tumor-promotive and tumor-suppressive secretomes, focusing on multi-tasking proteins in the intracellular and extracellular domains. We describe tumorigenic signaling that governs the nature of the tumor cell secretome and discuss the possibility of inducing tumor-suppressive proteomes as a novel option for cancer treatment. We evaluated the counterintuitive procedure to generate tumor-suppressive proteomes from a unique type of tumor-modifying cells, which are named "induced tumor-suppressing cells" (iTSCs).

Keywords: cancer; secretome; proteome; oncogene; tumor suppressor

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1. Introduction

Biological organs, tissues, and cells regulate their behaviors by a positive controller and a negative controller. Bone formation is regulated by bone-forming osteoblasts as an activator and bone-resorbing osteoclasts as an inhibitor [1]. The level of calcium in the blood is mainly elevated by parathyroid hormone and reduced by calcitonin [2]. Tumor cells are also regulated by tumor-promoting and suppressing regulators [3]. To eliminate cancer cells, chemotherapy is one of the most popularly utilized therapies in which chemotherapeutic drugs are targeted to DNA replication, cell cycling, and metabolic activities [4]. While these drugs can be applied alone or in combination, they carry a significant risk of side effects because of their inhibitory role in the cellular activities of both tumor and non-tumor cells [5]. An intriguing question is whether cancer cells can be killed not by the inhibition of cellular activities but by their activation. From the viewpoint of regulatory systems, both inhibitory and stimulatory drugs can be applied for blocking tumor progression. However, it is not a common practice to apply a drug that enhances the activities of

tumor suppressors. Although many tumorigenic pathways have been identified, drugs are generally inhibitors of those signalings such as Wnt, PI3K, PKA, etc. A provocative question is whether it is possible to activate oncogenic signalings and kill cancer cells. This review provides a positive answer to a paradoxical strategy of overexpressing oncogenes, focusing on the secretomes of tumor and non-tumor cells in the tumor microenvironment.

2. Tumor Cell Secretome and Chemotherapy

Most cells use their secretome to regulate the local and global environment, generally for the benefit of their growth and behaviors [6–8]. Tumor cells are not an exception and they secrete varying molecules to modify ECM for their adhesion and migration, stimulate angiogenesis for enhancing nutrient acquisition, remove neighboring cells for their room to expand, etc. [9–11]. Many lines of evidence also indicate that the tumor cell secretome is in general composed of varying tumor-promotive factors, including exosomes, metabolites, growth factors, lipids, and nucleic acids [12–15]. Ironically, it is also known that the administration of chemotherapeutic drugs such as vemurafenib [16], erlotinib [17], crizotinib [18], and BEZ235 [19] strengthens the tumorigenic capability of the tumor cell secretome. These drugs may initially remove tumor cells as well as non-tumor cells as a side effect, but tumor cells tend to develop drug resistance and the drugs eventually become ineffective [20–22]. It is also reported that the tumor-cell secretome includes IL-6, VEGF, TGFβ, IGF1, and EGF, which contribute to developing drug resistance in tumor cells [10,23,24]. Namely, their administration may assist the development of drug-resistant cells and the enhancement of the secretion of varying tumor-promoting factors [7,25]. Although chemotherapeutic agents constitute a primary set of cancer-fighting weaponry [26–28], the intent of suppressing tumor progression with inhibitory agents in chemotherapy may conversely end up strengthening the survival fitness of tumor cells.

3. Induced Tumor-suppressing Cells (iTSCs)

As a counterintuitive approach, an intriguing question is whether a tumor-suppressive secretome can be generated by administering an activator (and not an inhibitor in chemotherapy) of pro-tumorigenic signaling to tumor cells. Figure 1 depicts the two conceptual cases using the modulation of Wnt signaling as an example, the treatment with a chemotherapeutic inhibitor and that with an activator of tumor progression. In generating the conditioned medium that can be tumor-promotive or tumor-suppressive, tumor cells are typically incubated with the agent for one day. The actual examples using osteosarcoma cells and mammary tumor cells will be introduced later.

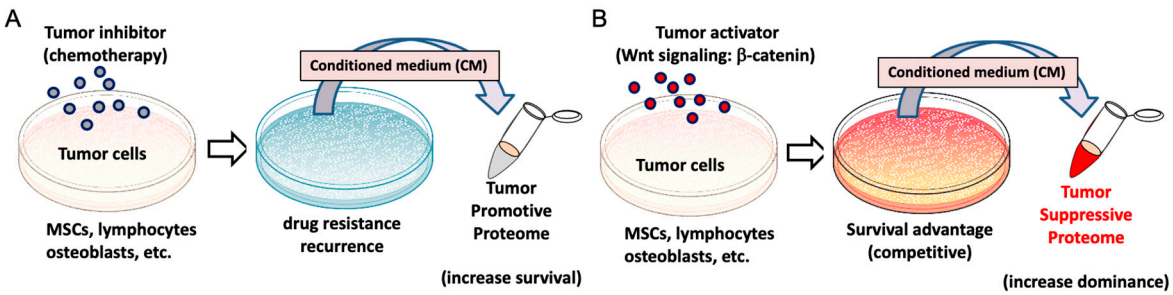

Figure 1. Comparison of the tumor-promotive secretome with the tumor-suppressive secretome. (**A**) Tumor cells induce the tumor-promotive secretome in response to a chemotherapeutic inhibitor to tumorigenic signalings, such as Wnt signaling, PI3K signaling, EMT induction, and PKA signaling [29,30]. Non-tumor cells (e.g., MSCs, lymphocytes, and osteoblasts, etc.) can also be used instead of tumor cells to produce a conditioned medium. (**B**) Tumor cells (and non-tumor cells, such as MSCs, lymphocytes, and osteoblasts, etc.) induce the tumor-suppressive secretome in response to an activator (e.g., the overexpression of β-catenin in Wnt signaling and the overexpression of Akt in PI3K signaling [29,30] to tumorigenic signaling).

To remove any remaining agents, the culture medium was exchanged by a fresh one and cells were cultured for an additional day. Then, the conditioned medium, which included tumor cell-secreted proteins, was characterized for its tumor-modifying features. Focusing on Wnt signaling, which is one of the targets to be inhibited in chemotherapy [31,32], a series of in vitro experiments were conducted to characterize tumor cell secretomes by overexpressing β-catenin [33] in breast cancer cells, prostate cancer cells, and pancreatic cancer cells. Remarkably, the result supported the tumor-suppressive capability of β-catenin-overexpressing tumor cell-derived conditioned medium (β-catenin CM) [29]. Of note, tumor secretomes are reported to be enriched with tumor-promoting factors, including proteins (e.g., VEGF) [34] and nucleic acids (e.g., PIK3CA and RASSF1A) [35].

Preclinical studies using a mouse model of mammary tumors and tumor-induced bone osteolysis also supported the tumor-suppressive, bone-protective capability of β-catenin CM. Those cells, which exhibited the tumor-suppressive capability by the activation of pro-oncogenic genes, were named "induced tumor-suppressing cells" (iTSCs) [29]. Figure 2 illustrates the unconventional concept with iTSC CM. The inoculation of tumor cells to a mouse induces a mammary tumor, and the injection of Wnt-activated tumor cells by the overexpression of β-catenin generates a larger mammary tumor. However, after the inoculation of tumor cells, the daily injection of β-catenin-overexpressing tumor cell-derived CM via a tail vein significantly reduces the size of mammary tumors. The administration of a control tumor cell-derived CM does not reduce the size of tumors. The result, for the first time, indicated the possibility of developing a novel therapeutic option that is based on a paradoxical concept of activating oncogenic signaling.

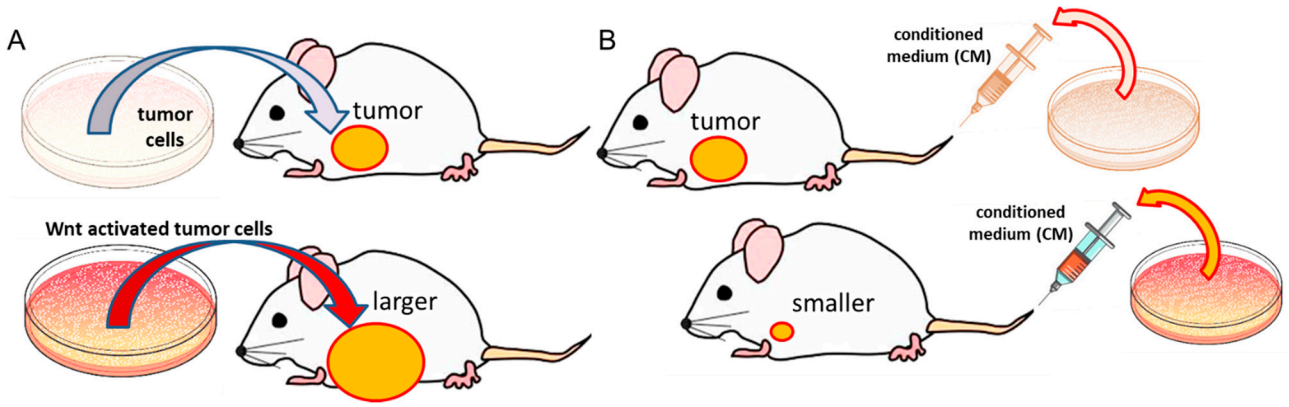

Figure 2. Counterintuitive reduction in mammary tumors by the administration of a Wnt-activated tumor cell-derived conditioned medium. (**A**) The inoculation of Wnt-activated tumor cells induces a larger mammary tumor than that of control tumor cells. (**B**) The administration of a Wnt-activated tumor cell-derived conditioned medium suppresses the growth of mammary tumors. In the study by Liu et al. [29], it is found that Lrp5-overexpressing osteocyte-derived conditioned medium significantly reduced the progression of mammary tumors as well as the destruction of the tumor-invaded tibia in a mouse model of breast cancer and bone metastasis. It is also reported by Sun et al. [30] that Akt-overexpressing MSC-derived conditioned medium inhibited the growth of mammary tumors and bone loss in the tumor-colonized tibia in a mouse model.

4. Generation of iTSCs from Non-Tumor Cells

The generation of iTSCs from tumor cells raised another question as to whether iTSCs can be created from non-tumor cells. The question was positively answered by the overexpression of β-catenin and Lrp5, a Wnt coreceptor, in mesenchymal stem cells (MSCs) [30]. The overexpression of β-catenin and Lrp5 generated MSC-derived iTSCs whose CM was able to suppress the progression of mammary tumors and the degradation of tumor-invaded bone in a mouse model. Besides the activation of Wnt signaling, the overexpression of Akt in PI3K signaling [36,37] and Snail in the induction of EMT [38,39] was able to generate MSC-derived iTSCs. Notably, osteocytes were also found to become iTSCs

by the overexpression of β-catenin and Lrp5 [40]. Interestingly, iTSCs can be generated not only by the overexpression of pro-tumorigenic genes but also by pharmacological agents such as an activator of Wnt signaling (e.g., BML284 [41]) and PI3K signaling (YS49 [42]). So far, no harmful iTSC cases have been reported in preclinical studies.

Figure 3 presents one example of inducing tumor-suppressive secretomes from T lymphocytes. In this example, Jurkat T-lymphocytes [43] were treated with a protein kinase A [44] (PKA) inhibitor, H-89 [45], as well as a PKA activator, CW008 [46]. One day after the incubation, lymphocytes were rinsed and the culture medium was replaced with a fresh one. The conditioned medium was collected after one-day incubation and they were given to U2OS human osteosarcoma [47] and EO771 mammary tumor cells [48]. The MTT-based metabolic activity, which indicates cell viability, was elevated by PKA inhibitor-treated CM and reduced by PKA activator-treated CM. This example supports the counterintuitive approach in which the tumor-suppressive secretomes were obtained by the activation of PKA signaling.

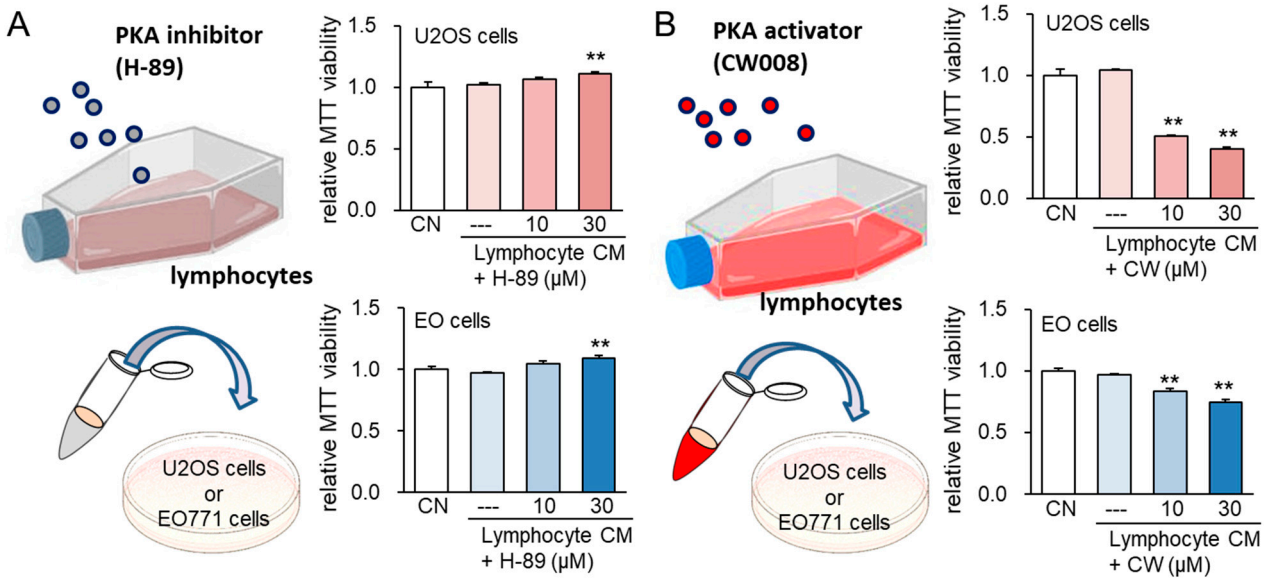

Figure 3. Alterations in metabolic activities in response to the inhibitor and activator of protein kinase A (PKA). In this experiment, Jurkat T lymphocytes were treated with H-89 and CW008 at10 and 30 μM (Tocris, Minneapolis, MN, USA). After 24 h, the medium was exchanged to remove H-89 or CW008. Cells were then incubated for 24 h for the collection of CM. CM was centrifuged at 2000 rpm for 10 min. Cell-free supernatants were centrifuged at 4000 rpm for 10 min and subjected to filtration with a 0.22-μm polyethersulfone membrane (Sigma; St. Louis, MO, USA). An MTT assay was conducted using U2OS osteosarcoma cells [47] and EO771 mammary tumor cells [48]. Tumor cells were seeded in 96-well plates (Corning; Glendale, Arizona, USA) and grown in CM for 2 days. Cells were dyed with 0.5 mg/mL thiazolyl blue tetrazolium bromide (Sigma) on day 4 for 4 h, and optical density for assessing metabolic activities was determined at 570 nm using a multi-well spectrophotometer. (**A**) H-89 (PKA inhibitor)-treated lymphocytes produce the pro-tumor conditioned medium that elevated MTT-based viability of U2OS osteosarcoma cells and EO771 mammary tumor cells. (**B**) CW008 (PKA activator)-treated lymphocytes produce the anti-tumor conditioned medium that reduced MTT-based viability of U2OS osteosarcoma cells and EO771 mammary tumor cells. ** $p < 0.01$.

5. Tumor Heterogeneity and Survival of the Fittest

A survival of the fittest is the dominating principle that is a basis for biodiversity at multiple levels including the biosphere, ecosystem, communities, populations, organisms, tissues, cells, and selfish DNA [49–52]. Cancer cell secretome can be viewed as a means for cancer cells to elevate their survival of the fittest [10,53–55]. In response to chemotherapy, tumor cells may synthesize tumor-promotive secretomes to elevate their survival in collaboration with neighboring tumor cells. In response to the activation of oncogenic signaling, tumor cells may choose to strengthen their dominance over others by eliminating neighbor-

ing tumor cells. It is reported that surgical removal of tumors occasionally resulted in the acceleration of tumor progression [56]. It is postulated that post-surgical tumor progression can be caused by surgery-linked injury and inflammatory responses, as well as the space created by the removal of the tumor [57]. Alternatively, this paradoxical outcome may be linked to tumor-driven anti-tumor capability, in which influential tumors may impede the progression of less-contentious tumors and their surgical removal could adversely affect the survival of patients. Interestingly, the inhibitory effect of iTSC CM is mostly selective to tumor cells rather than non-tumor cells [29]. The mechanism of the observed tumor selectivity should be further analyzed to lessen the current side effects of chemotherapeutic drugs. Alternatively, the observed variations among cancer cell secretomes may indicate the possibility of effective personalized cancer treatment [10].

6. Dependence on Cancer Types

Despite the significant development of therapeutic options during the past decades, chemotherapy remains the main method for cancer treatment. As the efficacy of chemotherapeutic agents differs depending on cancer types [58,59], further investigation is necessary to understand the therapeutic potential of iTSC-derived secretomes for varying types and subtypes of cancers. There are five major types of cancers, including carcinomas, sarcomas, melanomas, lymphomas, and leukemias [47]. The most frequently diagnosed cancers are carcinomas in the breast, prostate, pancreas, and lungs [48]. Sarcomas, such as osteosarcoma and chondrosarcoma, are cancers in the connective tissue, and melanomas arise from the pigment in the skin [60,61]. Lymphomas are cancers of lymphocytes, while leukemias are cancers of the blood [62,63]. The tumor microenvironment is largely different among the five major types of cancers and there are also differences in therapeutic response, drug resistance, and clinical outcome [64–66]. An important question is whether all types of cancers are responsive to iTSC CM and whether there are any differences in efficacy. Furthermore, another question is whether the progression of primary and secondary tumors is equally suppressed. Existing in vitro and in vivo studies support the suppression of cancer cell lines in the breast, prostate, pancreas, and bone [29,30]. No studies have been conducted for melanomas, lymphomas, and leukemias. Most data so far have been collected for breast cancer [29,30,40,67]. It has been found, using freshly isolated breast cancer tissues, that both estrogen receptor-positive and negative cancer tissues are responsive to iTSC-derived CM.

7. Source of iTSCs

The efficacy of iTSC CM also depends on the source of iTSCs. So far, iTSCs were generated from MLO-A5 osteocytes [68] and mouse and human MSCs, as well as tumor cells such as MDA-MB-231 breast cancer cells [69], EO771 mammary tumor cells [70], 4T1.2 mammary tumor cells [71], PC-3 prostate cancer cells [72], and PANC-1 pancreatic cancer cells [73]. An intriguing question is whether iTSCs can be generated from any type of cell that produces secretory proteins. From a translational viewpoint, it is desirable to generate iTSCs from cells that are accessible from a patient. For instance, MSCs may present considerable advantages over other cells for manufacturing, storage, handling, and their potential as ready-to-go biologic products [74]. Also, it is reported that peripheral blood mononuclear cells may present the benefit in regenerative medicine and tumor treatment [75]. It is interesting to know whether iTSCs can be generated from the bone marrow aspirates and peripheral blood. The existing data support that it is possible to generate iTSCs from bone marrow-derived MSCs and T lymphocytes in the peripheral blood.

8. Activation of Tumorigenic Signaling and Inhibition of Anti-tumorigenic Signaling

So far, iTSCs have been generated by the activation of tumorigenic signalings such as Wnt signaling, PI3K signaling, and the induction of EMT. There are many other tumorigenic pathways [76], including cell cycle [77], Hippo [78], Myc [79], Notch [80], NRF2 [81],

Ras [82], and TGFβ [83]. An obvious question is whether the activation of these pathways may generate iTSCs. The most effective way to induce iTSCs may depend on the oncogenic pathway to be activated and this pathway may differ for each type of source cells.

In generating iTSCs, two alternative procedures can be considered. One alternative procedure is the inactivation of anti-tumorigenic signaling. This is a logical prediction since the activation of tumorigenic signaling may result in a state that is equivalent to the inactivation of anti-tumorigenic signaling. For instance, AMP-activated protein kinase (AMPK), a serine/threonine protein kinase that regulates cellular energy homeostasis [84], is mainly considered ani-tumorigenic. It plays a vital role in cell metabolism and cell proliferation [85]. An activator of AMPK is reported to reduce the incidence of cancer [86,87]. AMPK inhibits tumor growth by inhibiting the mammalian target of rapamycin (mTOR) [88] and cyclooxygenase-2 (COX-2) [89], and by activating p53 [90]. AMPK is also reported to inhibit the integrin-dependent pathway that is known to promote tumor growth [91], through integrin β1 [92] and FAK and Src [93]. It is of interest to examine whether the inhibition of AMPK may generate iTSCs and tumor-suppressive secretomes. In addition to AMPK, there are anti-tumorigenic signaling proteins that may have a potential to generate iTSCs, including p53 [94], pRb [95], p21 [96], PTEN [97], and p16 [98].

The other formal possibility is the overexpression of tumor-suppressing proteins, such as p53 [99–101]. If p53-overexpressing cells can secrete p53 in the extracellular domain and extracellular p53 may suppress neighboring tumor cells, p53-overexpressing cells are considered iTSCs. Besides the overexpression of tumor-suppressing proteins, we cannot remove the possibility in which the inhibition of oncogenic signaling may generate iTSCs. For instance, the treatment of an inducer of tumor-suppressing proteins, which is considered to be an inhibition of oncogenic signaling, may generate iTSCs. Tumor suppressor genes regulate varying cellular processes, including cell cycling, DNA damage repair, protein degradation, and angiogenesis [102]. Further analysis is recommended to generate iTSCs without activating tumorigenic signaling.

9. Regulatory Mechanism and Moonlighting Proteins

The reported tumor-suppressing proteins, enriched in iTSC CM [29,30,67], include polyubiquitin C [103], enolase 1 [104], Hsp90ab1 [105], moesin [106], Eef2 [107], histone H4 [108], Vinculin [109], and isomerase B [110], and ubiquitin C [111]. Interestingly, many of these have been considered tumor-promoting proteins. Thus, as moonlight proteins, these proteins may function as a tumor suppressor in the extracellular domain in iTSC CM while a tumor promoter in the intracellular domain [112,113]. We have published mass spectrometry-based whole-genome proteomics data and presented atypical tumor-suppressing proteins [29,30,67]. For instance, it is demonstrated that recombinant proteins of enolase 1 and ubiquitin C inhibit the proliferation and migration of breast cancer cells, whereas its overexpression in breast cancer cells promotes their tumorigenic behaviors. Specifically, the interaction of enolase 1 with CD44 was involved in the downregulation of MMP9 [114], Runx2 [115], and Snail [116] in tumor cells [29]. Also, the activation of PI3K signaling in MSCs generated tumor-suppressive MSC CM that included the elevated level of cyclophilin B [30]. While extracellular cyclophilin B was found to act as a tumor suppressor in mammary tumors, its high expression in breast cancer is associated with malignant progression [117]. These observations raise a critical view on the current practice of inhibiting specific tumor-promoting proteins such as cyclophilin B, Eef2, enolase 1, Hsp90ab1, and ubiquitin C since their inhibition may also block their tumor-suppressing action. Further analysis is needed to clarify the regulatory mechanism underlying the action of atypical tumor-suppressing proteins in iTSC CM.

10. Translational Possibility of iTSC Secretomes

As a translational possibility, a patient may receive iTSC secretomes as an intravenous injection or iTSCs as autologous implantation. It has been found that iTSCs and their CM can be obtained from bone marrow-derived MSCs as well as T lymphocytes in the

peripheral blood. Since tumor-suppressive MSC CM was generated by the treatment of MSCs with YS49, an activator of PI3K signaling [30], it is not necessary to overexpress any genes. A pharmacological agent such as YS49 can easily be removed by filtration [118]. It is reported that the removal of exosomes elevated the tumor-suppressive capability [119], while our ongoing treatment with nucleases did not alter the anti-tumor action of iTSC CM. The detailed procedure to generate iTSCs, such as the selection and concentration of a pharmacological agent, the type and number of cells as a source of iTSCs, and culturing conditions and time, etc., should be carefully determined, and it may be custom-tailored to each patient.

iTSC CM can be administered as a complete or partially filtered form to a patient systemically or locally. A specific tumor-suppressing protein or a group of tumor-suppressing proteins might be given to a patient. This combinatorial administration can be custom-tailored for individual patients based on their types and stages of cancers. It is reported that matched therapy (precision medicine) is associated with superior outcomes, compared to non-matched therapy across tumor types and in specific cancers [120]. The mass production of secretomes from commercially available cell lines may present an alternative approach for the generation of iTSC CM [121,122].

11. Engineering the Anti-Tumor Secretomes

The secretion of anti-tumor secretomes can be augmented by targeting cellular components or controlling the extracellular microenvironment. The former includes genetically engineering the cells (gene transfer or gene editing), modifying cell surface receptors, or delivery of biologics intracellularly via engineered nanoparticles [123]. Many of these approaches have been established in altering secretomes of MSCs [124]). While directly altering intracellular signaling is a powerful approach to affect secretomes, accumulating evidence suggests that controlling the extracellular microenvironment may also dictate cell fate processes, which include changing the compositions of the secretomes [125]. In this regard, engineered biomaterials can provide desired cell-matrix interactions to improve cell survival and influence their secretory properties via mechanosensing or activating receptor-mediated signaling pathways [126]. Furthermore, conventional two-dimensional (2D) cell culture may not be adequate to maintain the desired anti-tumor secretomes and recent efforts in the design and engineering of 3D hydrogels may improve the anti-tumor secretory properties. It is reported that advanced hydrogel technology facilitates investigating the biophysical and biochemical cues impacting tumor microenvironments [127]. Uniquely, hydrogels can be engineered to support long-term cell culture in a physiologically relevant microenvironment [128]. Hydrogels can also directly influence secretomes via changing the biophysical and biochemical properties [129].

12. Sustained Delivery of Anti-Tumor Secretomes

Direct injection of anti-tumor CM is convenient but not practical from a translational standpoint. To this end, injectable polymeric protein carriers are uniquely suited for providing long-term delivery of anti-tumor secretomes [126]. Considering that many tumor sites are acidic, it will be ideal to develop a pH-responsive polymer carrier to achieve stimuli-responsive delivery of CM [130]. The application of carriers, which synergistically respond to pH/temperature, can improve the bioavailability and stability of CM, and extend the circulation time of CM. Ideally, the polymer carrier should be easily formulated with a CM payload for injectable delivery to the tumor/metastasis space [131]. Furthermore, the polymer carrier should protect the CM from proteolytic degradation and provide a mechanism for adaptive CM dosing that maximizes the therapeutic efficacy. These systems can be responsive polymers that are sensitive to heat, light, pH, redox, enzyme, magnetic field, ultrasound, hypoxia, etc. [132]. Ultimately, the sustained and controlled delivery of engineered cell-derived CM will pave the way for the development of personalized CM, where patient-derived cells are used to suppress the progression of primary and metastatic tumors.

13. Conclusions

The iTSC tumor-suppressive secretome is a mirror image of a chemotherapy-driven tumor-promotive secretome. While identifying a target to be inhibited and designing inhibitory drugs in chemotherapy is a prime task in the current drug development, identifying a target to be activated and designing stimulatory drugs to generate iTSCs could be an alternative possibility in cancer treatment. The efficacy of iTSC CM in preclinical studies is encouraging. It is worth planning a translational study from a bench side to bedside and testing its efficacy in clinical trials.

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